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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,218	02/01/2002	Katie (Mary) Binley	674523-2014	5329

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/066,218	BINLEY ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *31 May 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A preliminary amendment was received and entered on 5/20/02.

Claims 1-23 are pending and under consideration in the this Office Action.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in the UK on 1/31/02. It is noted, however, that applicant has not filed a certified copy of the foreign application as required by 35 U.S.C. 119(b). As such the priority date for the instant application is considered to be 2/1/02.

Claim Objections

Claim 1 is objected to because it contains the acronym HRE, but does not define it. Generally, Applicant should amend the first claim containing a given acronym to contain the full name of what is implied by the acronym. For example, claim 1 should be amended to contain the full name "hypoxia response element", and to include the acronym HRE parenthetically after the full name.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-14 are indefinite because it is unclear what are the metes and bounds of "corrected". The specification at paragraph 37 states:

> "[w]ith regard to the physiological correction and maintenance of the hematocrit level, it is meant for maintenance to encompass art-recognized treatment guidelines for chronic renal failure which seek to maintain hematocrit levels at 30-33% of the normal range of the hematocrit. (Kaufman et al. (1998) N Engl J Med 339: 578-583.) Normal levels of the hematocrit for males are 39-52%, and for females are 35-47%."

This is a non-limiting example of correction and maintenance which, while giving one example of what is embraced, does not set forth the metes and bounds of "corrected". Absent any clearer definition, one of skill in the art cannot know what degree of correction is required to meet the conditions of the claim. For example, is it required that the hematocrit must be corrected to within the normal ranges disclosed in the specification, or is it sufficient to attain any increase in hematocrit either above or below "normal"? This rejection could be overcome by limiting the hematocrit to a range of values that is supported by the specification.

Claims 1-23 are indefinite because the metes and bounds of "physiologically regulated" and "physiological regulation" are unclear. The only apparent definition of the term in the specification is set forth above in the previous paragraph. This definition is non-limiting and one of skill in the art cannot know the metes and bounds of the protection which Applicant seeks. The phrase physiological regulation could be interpreted to a variety of breadths. For example, it could mean simply that EPO is expressed in the appropriate tissues in vivo. Note that the claims do not require that the physiological regulation is conferred by the HRE. On the other hand the claims could be interpreted more narrowly as requiring that the vector provides expression of Epo

under hypoxic conditions. Absent a more precise definition, one of skill in the art cannot know the metes and bounds of the claims.

Claims 10, 11 and 15-23 are indefinite because they require that "the HRE expression control sequence includes two or more HRE expression control sequences". This is a contradiction in terms. A single object cannot comprise two or more of itself, because it is a single object. It follows that a "HRE expression control sequence" cannot comprise more than one "HRE expression control sequence". While it is clear from the teachings of Ratcliffe et al (US Patent 5,942,434 that sequences known as HREs may contain more than one HIF binding site (i.e. more than one site that confers hypoxia responsiveness), this is not what is referred to in the instant claims, and the structure of the claims as written renders them indefinite because they require a physical impossibility.

Claims 11 and 18-21 are indefinite because they recite "the HRE expression control sequence" without proper antecedent basis. Each of these claims depends from a claim requiring two or more HRE expression control sequences. It is unclear to which of these HRE expression control sequences claims 11 and 18-21 refer.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for transient maintenance of normal hematocrit levels

by administration of a vector comprising a nucleic acid encoding EPO operatively linked to a hypoxia sensitive promoter, wherein the viral vector is an adenovirus-associated virus (AAV) or a helper-dependent adenovirus vector in which the genome encodes no adenoviral antigens, does not reasonably provide enablement for maintenance of normal hematocrit levels through the direct administration of other vectors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for transient maintenance of normal hematocrit levels by administration of a vector comprising a nucleic acid encoding erythropoietin (Epo) operatively linked to a hypoxia sensitive promoter, does not reasonably provide enablement for permanent maintenance of normal hematocrit levels through such treatment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are directed to methods of treating anemia by administration to a patient of a vector comprising a nucleic acid encoding Epo operatively linked to a hypoxia responsive element, wherein the treatment results in correction and maintenance of hematocrit. levels. The claims do not limit the length of time that the hematocrit levels must be maintained.

The prior art teaches several examples of increasing hematocrit by deliver of vectors encoding Epo. Bohl et al (Blood (2000) 95(9): 2793-2798) taught correction of hematocrit in beta thalassemic anemic mice for at least one year by intramuscular delivery of AAV expression vectors for Epo. Payen et al (Exp. Hematol. (2001) 29(3) : 295-300) taught improvement in hematocrit in beta thalassemic anemic mice for at least 4 months by intramuscular electro-transfer of naked DNA encoding Epo. Hematocrit values declined linearly after 2 months, following a decline in Epo expression. and would indicate a return to control values at about 7 months if linearity persisted. See Figs. 2 and 3 on page 297. Rizzuto et al (Hum. Gene Therapy (2000) 11: 1891-1900) taught correction of anemia in partially nephrectomized rats by intramuscular electro-transfer of naked Epo expression vectors. Correction of hematocrit persisted for at least 5 weeks post-injection without significant reduction. See Fig. 5 on page 1897. In normal rats, electro-transfer of the same vector resulted in elevated hematocrit for at least 300 days, with hematocrit values maximal at 50 days and decreasing thereafter. See Fig. 4 on page 1896. Rudich et al (J. Surg. Res. (2000) 90(2): 102-108) taught expression of Epo in vivo in Cynomolgus monkeys by administration of an AAV vector encoding Epo. Expression decreased to background levels at about 41 weeks post-injection. See Fig. 1 on page 104. Osada et al (Kidney international (1999) 55: 1234-1240) taught correction of hematocrit in mice with renal anemia by delivery of an adenovirus vector encoding Epo. Correction was maintained for at least 40 days. See abstract and Fig. 6 on page 1239). Epo expression decreased after 20 days and approached control levels at 40 days. See Fig. 4 on page 1238. Finally, Savino et al (WO 00/09713, published

2/24/00) showed an increase in hematocrit following delivery to mice of hybrid adenovirus/AAV vectors encoding Epo. Hematocrits were elevated for greater than 225 days depending on the dosage of the vector, but declined following a decline in the levels of expressed Epo. See Fig. 4. In summary, the duration of Epo expression after gene delivery varies with the vector, but decreases over time after administration. As expected, hematocrit levels follow Epo levels with a delay that can be accounted for by the lifetime of red blood cells in circulation.

The specification teaches a working example in which anemic mice were treated with a single injection of 10^{10} AAV particles encoding Epo under the control of a hypoxia responsive promoter. The mice showed restoration of normal hematocrit for the duration of the study (it is not clear if this was 160 or 210 days, see page 34, lines 9-16, and sentence bridging pages 34 and 35). This is within the range reported in the prior art. The expression levels of Epo were not reported.

The specification provides no guidance as to how to prolong Epo expression from delivered vectors indefinitely.

In view of the state of the prior art, in which expression of delivered Epo genes was shown to be transient and not permanent, regardless of the type of delivery vector, and in view of the lack of any guidance in the specification as to how to prolong expression from these vectors, one of skill in the art would have to perform undue experimentation in order to achieve permanent correction of hematocrit using the methods of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1- 4, 7, 10, 12-18 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Savino et al (WO 00/09713, published 2/24/00).

Savino teaches a method of correcting and maintaining the hematocrit of an anemic patient by administering an adenoviral vector comprising a nucleic acid encoding Epo under the control of a promoter and hypoxia responsive elements from the Epo gene. See e.g. claims 1-11, and page 14, lines 1-7. The patient may be a human, other primate, canine, feline, bovine, equine, ovine, or porcine mammal. See page 15, lines 16-18. This adenoviral vector is also considered to be an adeno-associated viral (AAV) vector because it comprises the expression construct inserted between AAV ITRs. See example 1 at pages 24-27, especially paragraph bridging pages 26 and 27. As such the vector comprises the minimal sequences necessary for rescue, replication, packaging, and integration of an AAV genome.

Thus Savino anticipates the claims.

Claims 1- 4, 7, 10, 12-18 and 21 are rejected under 35 U.S.C. 102(e) as being anticipated by Savino et al (US Patent 6,641,807, issued 11/4/03).

Savino teaches a method of correcting and maintaining the hematocrit of an anemic patient by administering an adenoviral vector comprising a nucleic acid encoding Epo under the control of a promoter and hypoxia responsive elements from the Epo gene. See e.g. claims 1-4, and column 6, lines 4-10. The patient may be a human, other primate, canine, feline, bovine, equine, ovine, or porcine mammal. See column 6, lines 37-44, and claims 1-4. This adenoviral vector is also considered to be an adeno-associated viral (AAV) vector because it comprises the expression construct inserted between AAV ITRs. See column 10, line 1 to column 11, line 30, especially paragraph bridging columns 10 and 11. As such the vector comprises the minimal sequences necessary for rescue, replication, packaging, and integration of an AAV genome.

Thus Savino anticipates the claims.

Claims 15, 19, and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Rinsch et al (Human Gene Therapy (1997) 8(16): 1881-1889).

Rinsch teaches a vector comprising the mouse PGK-1 promoter, including hypoxia responsive enhancer sequences, operably linked to a human Epo cDNA., that provides physiological regulation of Epo expression when administered to a host. See abstract, page 1882, column 1, lines 4-9 of first full paragraph, and Fig. 1.

Thus Rinsch anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8 and 10-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Savino et al (WO 00/09713, published 2/24/00) in view of Ratcliffe et al (US Patent 5,942,434, issued 8/24/99).

Savino teaches methods of correcting and maintaining the hematocrit of an anemic patient by administering an adenoviral vector comprising a nucleic acid encoding Epo operably linked to a promoter and hypoxia responsive elements from an Epo gene. See e.g. claims 1-11, and page 14, lines 1-7. The patient may be a human, other primate, canine, feline, bovine, equine, ovine, or porcine mammal. See page 15, lines 16-18. The adenoviral vector is also considered to be an adeno-associated viral (AAV) vector because it comprises the expression construct inserted between AAV ITRs. See example 1 at pages 24-27, especially paragraph bridging pages 26 and 27. As such the vector comprises the minimal sequences necessary for rescue, replication, packaging, and integration of an AAV genome.

Savino does not teach an expression construct comprising a PGK-1 or LDH-A HRE, or a construct comprising an HRE in combination with a viral promoter.

Ratcliffe teaches that the Epo, PGK-1, and LDH-A promoters are inducible by hypoxia, and can be linked to genes that one wishes to express under conditions of hypoxia. These promoters comprise HREs. Ratcliffe also exemplifies hybrid promoters which have been rendered hypoxia sensitive through linkage to one or more of these HREs. See e.g. abstract; column 3, lines 22-67, especially, lines 61-67; and column 5, lines 51 and 52. Examples of hybrid promoters include a promoter comprising 1-5 copies of an Epo HRE linked to an SV40 viral promoter, and a promoter comprising 3 copies of a PGK HRE linked to a viral thymidine kinase promoter. See e.g. column 5, lines 27-49 and column 10, lines 1-31.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the hypoxia-induced promoters of Ratcliffe in the expression constructs and methods of Savino because Savino teaches that hypoxia inducible promoters in general may be used in the invention. See column 6, lines 4-10. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case, all of the

promoters of Ratcliffe satisfy the criterion of being hypoxia inducible, and so are art recognized equivalents in this regard.

Claims 9 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Savino et al (WO 00/09713, published 2/24/00) and Ratcliffe et al (US Patent 5,942,434, issued 8/24/99), as applied to claims 1-6, 8, 10, 11, and 13-22 above, and further in view of Yurchenko (US Patent 6,632,790 issued 10/14/03).

The teachings of Savino and Ratcliffe are summarized above and can be combined to render obvious methods of correcting and maintaining the hematocrit of an anemic patient by administration of vector systems comprising one or more HRE elements in operable linkage with a viral (SV40) promoter and an Epo cDNA.

These references do not teach a construct comprising an HRE and a CMV promoter.

Yurchenko indicates that SV40 and CMV promoters may be substituted for one another in gene expression constructs. See column 12, lines 45-51.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the CMV promoter of Yurchenko for the SV40 promoter of Ratcliffe and to use the resulting hybrid promoter in the expression vector and methods of Savino. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such

substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case, Yurchenko teaches that SV40 and CMV promoters are interchangeable, so there is no reason to believe that the CMV promoter could not be substituted for the SV40 promoter in the hybrid constructs of Ratcliffe, and subsequently used in the invention of Savino.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441 until 1/13/04, and thereafter will be 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at 703-306-3217 before 2/22/04, and at 571-272-0811 after 2/22/04. The official central fax number is 703-872-9306 until further notice. Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413 prior to 1/14/04, and thereafter will be 571-272-0564.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.